UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/646,308	08/21/2003	Paul B. J. Burton	3432-US-NP	9578

22932 7590 09/18/2008

IMMUNEX CORPORATION
LAW DEPARTMENT
1201 AMGEN COURT WEST
SEATTLE, WA 98119

EXAMINER	
JIANG, DONG	
ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
09/18/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/646,308	BURTON ET AL.	
	Examiner	Art Unit	
	DONG JIANG	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *31-53 and 55-67* is/are pending in the application.

4a) Of the above claim(s) *31-45,53 and 55-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *46-52 and 63-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *31-53 and 55-67* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicant's amendment filed on 14 May 2008 is acknowledged and entered. Following the amendment, claim 54 is canceled, claims 46-48, 50 and 51 are amended, and the new claims 63-67 are added.

Currently, claims 31-53 and 55-67 are pending, and claims 46-52 and 63-67 are under consideration. Claims 31-45, 53 and 55-62 remain withdrawn from further consideration as being drawn to a non-elected invention.

Withdrawal of Objections and Rejections:

All objections and rejections of claim 54 are moot as the applicant has canceled the claim.

Rejections under 35 U.S.C. §112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 67 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 67 is indefinite for missing the number for the SEQ ID NO:. The metes and bounds of the claim, therefore, cannot be determined.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46-52 and 63-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for claims limited in scope to a method for reducing chronic

cardiotoxicity caused by a chemotherapeutic agent with a 4-1BB antagonist, does not reasonably provide enablement for claims to a method for *preventing* chronic cardiotoxicity caused by a chemotherapeutic agent with a 4-1BB antagonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The independent claim 46 recites a method for *preventing* or reducing chronic cardiotoxicity caused by a chemotherapeutic agent with a 4-1BB antagonist, wherein the limitation "preventing" reads on to keep the chronic cardiotoxicity from happening. While the specification teaches that a soluble receptor of m4-1BB-Fc delayed and reduced cardiac dysfunction (page 80, Table 4) when used prior to the administration of the chemotherapeutic agent adriamycin, it dose not show any evidence that a 4-1BB antagonist such as m4-1BB-Fc could prevent cardiac dysfunction from happening. Further, in searching the prior art, the results of record have not established that chronic cardiotoxicity caused by a chemotherapeutic can be prevented by a 4-1BB antagonist. Furthermore, the specification provides no instruction or guidance, nor working examples regarding the preventing effect of a 4-1BB antagonist on said chronic cardiotoxicity. Therefore, the asserted use for *preventing* chronic cardiotoxicity is not enabled.

Due to the large quantity of experimentation necessary to determine the preventing effect of a 4-1BB antagonist on said cardiotoxicity; the lack of direction/guidance presented in the specification regarding same; the absence of working examples directed to same; the complex nature of the invention; the state of the prior art, which has not established that said condition can be prevented by antagonizing 4-1BB; and the breadth of the claims which embraces preventative effect of a 4-1BB antagonist, undue experimentation would be required of the skilled artisan to use the claimed invention in its full scope.

Claims 46-49 and 52 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record set forth in the last Office Action mailed on 15 November 2007, at pages 3-5.

Applicants argument filed on 14 May 2008 has been fully considered, but is not deemed persuasive for the reasons below.

At page 10 of the response, the applicant argues that multiple forms of antagonist are described in the specification, for example, a soluble 4-1BB-L, polypeptide mimetics, such as peptidomimetics based on SEQ ID NO: 18 (4-1BB) and SEQ ID NO: 16 (4-1BB-L), muteins and variants including PEGylated peptides, oligomeric forms of 4-1BB, and antisense RNA and DNA molecules. This argument is not persuasive because, according to the specification, a 4-1BB antagonist is defined herein as an entity that is capable of reducing the effective amount of available endogenous 4-1BB and/or 4-1BB ligand (4-1BB-L) (page 15, lines 26-27), which defines the molecule by a functional property, and reads on any or all functional equivalent. Further, the specification teaches molecules that bind 4-1BB or 4-1BB-L and inhibit the interaction thereof, such as 4-1BB and/or 4-1BB-L small molecules, peptidomimetics and/or mimotopes, and/or polypeptides comprising all or portions of 4-1BB or 4-1BB-L or modified variants thereof, including genetically-modified muteins, multimeric forms and sustained-release formulations thereof (page 15, line 37 to page 16, line 3). Thus, the claims encompass significant structural dissimilarity as compared to the exemplified antibodies to 4-1BB or 4-1BB-L or modified variants thereof, and the soluble 4-1BB as no structure limitation is required for the antagonist. Further, with respect to other diverse molecules such as peptidomimetics, mimotopes, and small chemical molecules, although the terms are mentioned in the specification, none of them were ever identified or particularly described. The structures of these molecules are not predictable, thus, a skilled artisan cannot envision the detailed chemical structure of the encompassed "4-1BB antagonist". One cannot describe what one has not conceived, and the compound itself is required. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. Applicants further argue that Example 7 demonstrates the

relationship between antagonizing 4-1BB and reducing chronic cardiotoxicity caused by a chemotherapeutic agent in a subject, without limitation to a particular antagonist, therefore, the method as recited in claim 46 does not need to be restricted to a particular antagonist. This argument is not persuasive because the issue is not whether the antagonist as a whole (genus) is enabled in the claimed method, rather, the issue is that the genus is not well described, and a skilled artisan cannot envision the detailed chemical structure of the encompassed "4-1BB antagonist". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 46-52 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Yudestad et al. (Cardiovasc Res., 2002 Apr; 54(1):175-82, provided by applicants), and Goodwin et al. (US5,674,704, provided by applicants), and in view of Waelti (US2004/0028687), for the reasons of record set forth in the last Office Action mailed on 15 November 2007, at pages 3-5.

Applicants argument filed on 14 May 2008 has been fully considered, but is not deemed persuasive for the reasons below.

At pages 11-12 of the response, the applicant argues that Yndestad describes increased gene expression of a large number of molecules, that Yndestad also provides evidence that antagonizing TNF does not actually work in vivo, for example, soluble TNF-R did not reduce IL-6 levels in myocardium in animal studies, and a soluble TNF-type 2 molecule failed to be efficacious in two clinical trials. Applicants further argue that there is nothing in the reference to Yndestad to indicate to one of ordinary skill in the art that 4-1BB in particular would be the "obvious" target for therapeutic antagonists from among all of the other molecules identified, on the contrary, 4-1BB would appear to be the least likely target from the results shown in this reference, as it was not mentioned (like other TNF family members) in two experiments. This argument is not persuasive because lack of evidence of beneficial effects of TNF antagonists on CHF is, by no means, a predictor of the same for antagonists of 4-1BB or other molecules. Further, a reference is not limited to the disclosure of specific working examples, and all disclosures in the reference must be evaluated, including nonpreferred embodiments. Although 4-1BB was not included in the two experiments, the reference clearly teaches that 4-1BB-L is among those of several TNF superfamily ligands which gene expression is increased in CHF.

At page 12 of the response, the applicant argues that there was no discussion in the Yndestad reference of preventing or reducing chronic cardiotoxicity due to a chemotherapeutic agent, and there is nothing in this publication to suggest that antagonizing 4-1BB alone would prevent or reduce cardiotoxicity due to chemotherapeutic treatment, and that 4-1BB was not known to be expressed in the heart, and 4-1BB-L was not known to produce apoptosis of cardiac cells, according to this paper. This argument is not persuasive because although Yndestad does not teach preventing or reducing chronic cardiotoxicity due to a chemotherapeutic agent, it is the combined teachings of the references, which made the instant invention obvious. Further, whether 4-1BB was known to be expressed in the heart, or what was the mechanism of 4-1BB in causing said cardiotoxicity is less relevant because it was not necessarily a direct effect. Applicants further argue that there is no description or suggestion of antagonizing 4-1BB to treat chronic cardiotoxicity or cardiomyopathy in US5,674,704 (Goodwin reference), these two references appear to be completely unrelated; and that the Waelti reference does not mention 4-

1BB or 4-1BB-L nor provide any suggestion that antagonizing 4-1BB would prevent or reduce cardiotoxicity, therefore, it would not be *obvious* to one of ordinary skill in the art, based on Yndestad and Goodwin, in view of Waelti that antagonizing 4-1BB alone would prevent or reduce cardiotoxicity caused by a chemotherapeutic agent. This argument is not persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Yudestad expressly teaches that 4-1BB-L is among those of several TNF superfamily ligands which gene expression is upregulated in CHF; that *in particular*, the enhanced expression of ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in the progression of CHF. Further, Yudestad emphasizes that in particular, while not necessarily the initial event or the primary cause of CHF, the enhanced expression of ligands in the TNF superfamily may reflect a potential pathogenic role of these cytokines in the progression of this disorder (page 181, 1st column, the last sentence), providing clear motivation to try to antagonizing 4-1BB or 4-1BB-L for CHF. The Goodwin reference teaches soluble 4-1BB polypeptides, which retain the ability to bind the 4-1BB ligand; and Waelti teaches that anthracycline compounds, such as doxorubicin, have a very wide spectrum of anticancer activity, but their side effects include, among others, dose-dependent cardiotoxicity often resulting in irreversible cardiomyopathy with serious congestive heart failure. Therefore, it is obvious to use Goodwin's soluble 4-1BB polypeptides having the ability of binding the 4-1BB ligand in patients treated with doxorubicin in order to reduce the cardiotoxicity such as CHF as 4-1BB is indicated to have a potential pathogenic role in CHF.

Conclusion:

No claim is allowed.

Advisory Information:

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 571-272-0872. The examiner can normally be reached on Monday - Friday from 9:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Dong Jiang/, Ph.D.
Primary Examiner, Art Unit 1646
9/8/08